Integration of Nonclinical Genomic Study Data in Safety Assessment

John K. Leighton, PH.D., DABT
Division of Oncology Drug Products
CDER/FDA

Disclaimer

This presentation represents the current thinking of the pharmacology/toxicology review group of FDA's Center for Drug Evaluation and Research (CDER) in integrating genomic study data into nonclinical safety assessment. This approach may be modified based on new scientific developments or policy initiatives in this rapidly changing field.

Overview

- FDA's Strategic Plan
- Reporting requirements for nonclinical studies
- Genomics and safety assessment
- Initiatives/issues that need to be addressed

Goals of FDA's Strategic Plan

- Efficient, science-based risk management
- Patient and consumer safety
- Better informed consumers
- Counterterrorism
- A strong FDA

Nonclinical IND/NDA Studies

- Pharmacodynamics/Pharmacology
- Pharmacokinetics
- Safety pharmacology
- General Toxicology
- Genetic toxicity
- Reproductive toxicity
- Carcinogenicity

Reporting requirements: FD &C Act

- …the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, or preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing.

- …full reports of investigations which have been made to show whether of not such drug is safe for use and whether such drug is effective in use.

IND Submission requirements: 21 CFR 312.23(a) (8)

- Pharmacology and toxicology information “on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations”

- Guidelines available that describe ways in which these requirements may be met.

IND Submission requirements: continued

- Pharmacology:
  - describe the pharmacological effects and mechanism of action in animals
- Toxicology:
  - an integrated summary of the toxicological effects of the drug in animals and in vitro.
  - Full tabulation of data suitable for detailed review for studies intended primarily to support safety of proposed clinical trial.

Genomics and Safety Assessment

Genomics Technology

- Promise
  - Shorten drug development time
  - Enhance safety evaluation
  - Improve efficacy evaluation
- Concern
  - Incomplete understanding of the findings leading to adverse regulatory outcome
  - Lack of reviewer training
  - Differences/inconsistencies among review Divisions

Key Developments

- Initiation of FDA, CDER workgroups 2001
- First FDA/Phrma Workshop, May 2002
  - Report published, Lesko et al., J Clin Pharmacol 2003; 43:342-58
- CDRH Draft guidance, April 2003
- Advisory Committee Meeting, June 2003
- Second FDA/Phrma Workshop Nov 2003
- See also Petricoin et al., Nat Genetics 2002 Dec; 32 Suppl, 474-79

First Workshop

- Goals
  - Use of genomic technology in nonclinical and clinical drug development
  - Issues, limitations and questions related to the application of the technology
  - Future direction of regulatory policy and guidance for industry.
- Outcome
  - Recognition that toxicogenomics was not ready for routine use in regulatory decision making

"Safe Harbor" Issues

- Concept introduced @ May 16/17 2002 Workshop
- Regulatory authorities interested in enabling "-omics" technologies
- Regulators want to see and work with the data
- Sponsors concerned about premature regulatory actions
- "Safe Harbor": mechanism for submitted data not to be formally reviewed until better understood
- Submission allows accumulated experience to better understand data and integrate knowledge
- Now: Genomic Data Submission

Guidance

- CDRH draft guidance: **Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns; Draft Guidance for Industry and FDA Reviewers (4/21/03)**
- Goal: establish a set of recommendations to define the levels of data needed to establish a reasonable assurance of safety and effectiveness of a device
- http://www.fda.gov/cdrh/oivd/guidance/1210.pdf

Advisory Committee Questions

- Should the FDA/CDER be proactive at this time in enabling the incorporation of such study data into nonclinical phases of drug development, and in clarifying how the results should be submitted to the agency?

- What should the goals be for use of the data by CDER, and what major obstacles are expected for incorporating these data into nonclinical regulatory studies?

Advisory Committee Questions

- Is it: (a) feasible, (b) reasonable, and (c) necessary for CDER to set a goal of developing an internal database to capture gene expression and associated phenotypic outcome data from nonclinical studies in order to enhance institutional knowledge and realize the data's full value?

- What specific advice do you have to CDER for clarifying recommendations on data processing and analysis, as well as data submission content and format?

Second Workshop

- Pharmacogenomics and pharmacogenetics in drug development and regulatory decision making
- Nov, 2003: currently in planning
- Goals
  - Discuss The Genomic Data Submission (GDS) Proposal
    - » Voluntary submission
    - » Required submission
  - Case studies
  - Topic areas: nonclinical, clinical, clinical pharmacology
  - Develop a format and process for submitting and reviewing GDS
  - Gather input on the Agency's intent to develop a guidance

Genomic Experience to Date

- Agency and Center workgroups formed
- Share data as learning experience
  - Several IND submissions to date
  - Electronic data sets – “mock submission” – linked to toxicology data
- Limited access to proprietary databases

Future Directions

Questions

- When/how to use developing PG information in regulatory decisions?
- When is the information "reasonably applicable" to safety?"
- Under what circumstances is submission to FDA needed? Who determines submission requirement?

Possible Procedures

- FDA would establish Interdisciplinary PG Review Group (IPGRG)
- Categorization of studies and internal procedures published in guidance
- Results submitted to IND or NDA as "research information package" for review by IPGRG
- Periodic public re-evaluation of decision tree

Recent Scientific Initiative: Cross-platform comparison

- Goal: to identify a common set of genes that may be useful in comparing datasets generated with different platforms
- Model: search expression analysis experiments from databases of control samples to identify:
  - Genes uniquely expressed in various tissues
  - Genes similarly expressed in various tissues
- Tissues to be analyzed
  - Male liver, kidney, brain, testes
  - Assess performance of different tissue ratios
- Partner with stakeholders

Issues to be Addressed

- Format of pharmacology/toxicology genomic data submission
- Database development
  - Infrastructure requirements
  - Gene ontology issues
  - “Mock submissions” as learning tools
  - Reviewer training

Summary

- Different submission format for pivotal safety data.
- Guidance to describe what and how to submit.
- Good review practices for evaluation of data; provides consistency among review divisions and transparency.
- Review may need to consider interdisciplinary review of genomic data.
- Utilize Advisory Committees
- Genomics may play an important role in safety assessment in future INDs and NDAs.